

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

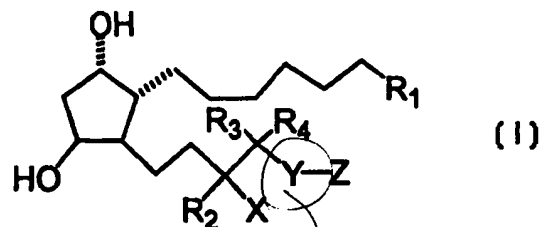
## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : <b>C07C 405/00 // A61K 31/557</b>	<b>A1</b>	(11) International Publication Number: <b>WO 99/12896</b> (43) International Publication Date: <b>18 March 1999 (18.03.99)</b>
<p>(21) International Application Number: <b>PCT/US98/18340</b></p> <p>(22) International Filing Date: <b>4 September 1998 (04.09.98)</b></p> <p>(30) Priority Data: <b>60/058,246</b>      <b>9 September 1997 (09.09.97)</b>      <b>US</b></p> <p>(71) Applicant: <b>THE PROCTER &amp; GAMBLE COMPANY</b> [US/US]; One Procter &amp; Gamble Plaza, Cincinnati, OH 45202 (US).</p> <p>(72) Inventors: <b>WOS, John, August</b>; 8505 Harperpoint Drive, Cincinnati, OH 45249 (US). <b>deLONG, Mitchell, Anthony</b>; 8084 Tyler's Circle, West Chester, OH 45069 (US). <b>AM-BURGEY, Jack, S., Jr.</b>; 265 Stockton Drive, Loveland, OH 45140 (US). <b>DE, Biswanath</b>; 11269 Cornell Woods Drive, Cincinnati, OH 45241 (US). <b>DAI, Haiyan, George</b>; 47-2 Revere Road, Drexel Hill, PA 19026 (US). <b>MILEY, Cynthia, J.</b>; 19 Bonham Road, Wyoming, OH 45215 (US).</p> <p>(74) Agents: <b>REED, T., David et al.</b>; The Procter &amp; Gamble Company, 5299 Spring Grove Avenue, Cincinnati, OH 45217-1087 (US).</p>	<p>(81) Designated States: AL, AM, AT, AT (Utility model), AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, CZ (Utility model), DE, DE (Utility model), DK, DK (Utility model), EE, EE (Utility model), ES, FI, FI (Utility model), GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (Utility model), SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b> With international search report.</p>	

(54) Title: AROMATIC C<sub>16</sub>-C<sub>20</sub>-SUBSTITUTED TETRAHYDRO PROSTAGLANDINS USEFUL AS FP AGONISTS

## (57) Abstract

The invention provides novel PGF analogs. In particular, the present invention relates to compounds having a structure according to formula (I) wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, X, Y, and Z are defined below. This invention also includes optical isomers, diastereomers and enantiomers of said formula, and pharmaceutically-acceptable salts, biohydrolyzable amides, esters, and imides thereof. The compounds of the present invention are useful for the treatment of a variety of diseases and conditions, such as bone disorders and glaucoma. Accordingly, the invention further provides pharmaceutical compositions comprising these compounds. The invention still further provides methods of treatment for bone disorders and glaucoma using these compounds or the compositions containing them.



methylene  
Carbon "unit"  
(CH<sub>2</sub>)

pick one  
change defn Y

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

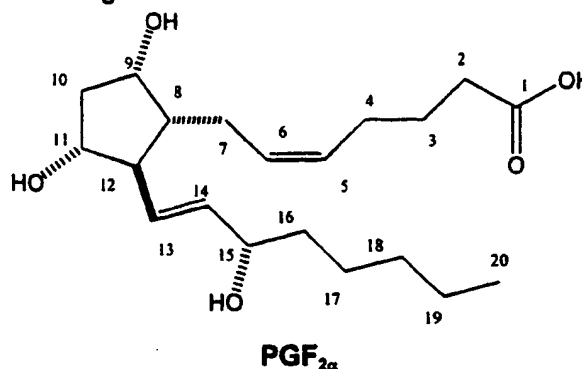
## AROMATIC C<sub>16</sub> - C<sub>20</sub> - SUBSTITUTED TETRAHYDRO PROSTAGLANDINS USEFUL AS FP AGONISTS

### TECHNICAL FIELD

The subject invention relates to certain novel analogs of the naturally occurring prostaglandins. Specifically, the subject invention relates to novel Prostaglandin F analogs. The subject invention further relates to methods of using said novel Prostaglandin F analogs. Preferred uses include methods of treating bone disorders and glaucoma.

### BACKGROUND OF THE INVENTION

Naturally occurring prostaglandins (PGA, PGB, PGE, PGF, and PGI) are C-20 unsaturated fatty acids. PGF<sub>2α</sub>, the naturally occurring Prostaglandin F in humans, is characterized by hydroxyl groups at the C<sub>9</sub> and C<sub>11</sub> positions on the alicyclic ring, a cis-double bond between C<sub>5</sub> and C<sub>6</sub>, and a trans-double bond between C<sub>13</sub> and C<sub>14</sub>. Thus PGF<sub>2α</sub> has the following formula:



Analogues of naturally occurring Prostaglandin F have been disclosed in the art. For example, see U.S. Patent No. 4,024,179 issued to Bindra and Johnson on May 17, 1977; German Patent No. DT-002,460,990 issued to Beck, Lerch, Seeger, and Teufel published on July 1, 1976; U.S. Patent No. 4,128,720 issued to Hayashi, Kori, and Miyake on December 5, 1978; U.S. Patent No. 4,011,262 issued to Hess, Johnson, Bindra, and Schaaf on March 8, 1977; U.S. Patent No. 3,776,938 issued to Bergstrom and Sjovall on December 4, 1973; P.W. Collins and S. W. Djuric, "Synthesis of Therapeutically Useful Prostaglandin and Prostacyclin Analogs", Chem. Rev. Vol. 93 (1993), pp. 1533-1564; G. L. Bundy and F. H. Lincoln, "Synthesis of 17-Phenyl-18,19,20-Trinorprostaglandins: I. The PG<sub>1</sub> Series", Prostaglandins, Vol. 9 No. 1 (1975), pp. 1-4; W. Bartman, G. Beck, U. Lerch, H. Teufel, and B. Scholkens, "Luteolytic

Prostaglandins: Synthesis and Biological Activity", Prostaglandins, Vol. 17 No. 2 (1979), pp. 301-311; C. Liljebris, G. Selen, B. Resul, J. Sternschantz, and U. Hacksell, "Derivatives of 17- Phenyl-18,19,20-trinorprostaglandin F<sub>2</sub> $\alpha$  Isopropyl Ester: Potential Antiglaucoma Agents", Journal of Medicinal Chemistry, Vol. 38 No. 2 (1995), pp. 289-304.

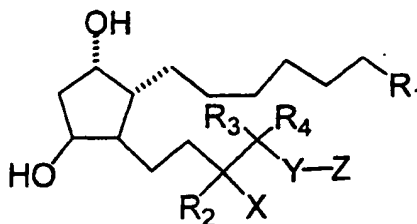
Naturally occurring prostaglandins are known to possess a wide range of pharmacological properties. For example, prostaglandins have been shown to: relax smooth muscle, which results in vasodilatation and bronchodilatation, to inhibit gastric acid secretion, to inhibit platelet aggregation, to reduce intraocular pressure, and to induce labor. Although naturally occurring prostaglandins are characterized by their activity against a particular prostaglandin receptor, they generally are not specific for any one prostaglandin receptor. Therefore, naturally-occurring prostaglandins are known to cause side effects such as inflammation, as well as surface irritation when administered systemically. It is generally believed that the rapid metabolism of the naturally occurring prostaglandins following their release in the body limits some of the effects of the prostaglandin to a local area. This effectively prevents the prostaglandin from stimulating prostaglandin receptors throughout the body and causing the effects seen with the systemic administration of naturally occurring prostaglandins.

Prostaglandins, especially prostaglandins of the E series (PGE), are known to be potent stimulators of bone resorption. PGF<sub>2 $\alpha$</sub>  has also been shown to be a stimulator of bone resorption but not as potent as PGE<sub>2</sub>. Also, it has been demonstrated the PGF<sub>2 $\alpha$</sub>  has little effect on bone formation. It has been suggested that some of the effects of PGF<sub>2 $\alpha$</sub>  on bone resorption, formation and cell replication may be mediated by an increase in endogenous PGE<sub>2</sub> production.

In view of both the wide range of pharmacological properties of naturally occurring prostaglandins and of the side effects seen with the systemic administration of these naturally occurring prostaglandins, attempts have been made to prepare analogs to the naturally occurring prostaglandins that are selective for a specific receptor or receptors. A number of such analogs have been disclosed in the art. Though a variety of prostaglandin analogs have been disclosed, there is a continuing need for potent, selective prostaglandin analogs for the treatment of a variety diseases and conditions.

### SUMMARY OF THE INVENTION

The invention provides novel PGF analogs. In particular, the present invention relates to compounds having a structure according to the following formula:



wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $X$ ,  $Y$ , and  $Z$  are defined below.

This invention also includes optical isomers, diastereomers and enantiomers of the formula above, and pharmaceutically-acceptable salts, biohydrolyzable amides, esters, and imides thereof.

The compounds of the present invention are useful for the treatment of a variety of diseases and conditions, such as bone disorders and glaucoma. Accordingly, the invention further provides pharmaceutical compositions comprising these compounds. The invention still further provides methods of treatment for bone disorders and glaucoma using these compounds or the compositions containing them.

## DETAILED DESCRIPTION OF THE INVENTION

### Terms and Definitions

"Acyl" is a group suitable for acylating a nitrogen atom to form an amide or carbamate or an oxygen atom to form an ester group. Preferred acyl groups include benzoyl, acetyl, tert-butyl acetyl, para-phenyl benzoyl, and trifluoroacetyl. More preferred acyl groups include acetyl and benzoyl. The most preferred acyl group is acetyl.

"Alkyl" is a saturated or unsaturated hydrocarbon chain having 1 to 18 carbon atoms, preferably 1 to 12, more preferably 1 to 6, more preferably still 1 to 4 carbon atoms. Alkyl chains may be straight or branched. Preferred branched alkyl have one or two branches, preferably one branch. Preferred alkyl are saturated. Unsaturated alkyl have one or more double bonds and/or one or more triple bonds. Preferred unsaturated alkyl have one or two double bonds or one triple bond, more preferably one double bond. Alkyl chains may be unsubstituted or substituted with from 1 to 4 substituents. Preferred alkyl are unsubstituted. Preferred substituted alkyl are mono-, di-, or trisubstituted. Preferred alkyl substituents include methyl, ethyl, propyl and butyl, halo, hydroxy, alkoxy (e.g., methoxy, ethoxy, propoxy, butoxy, pentoxy), aryloxy (e.g., phenoxy, chlorophenoxy, tolyloxy, methoxyphenoxy, benzyloxy, alkyloxycarbonylphenoxy, acyloxyphenoxy), acyloxy (e.g., propionyloxy, benzoyloxy, acetoxo), carbamoyloxy, carboxy, mercapto, alkylthio, acylthio, arylthio (e.g., phenylthio,

chlorophenylthio, alkylphenylthio, alkoxyphenylthio, benzylthio, alkyloxycarbonylphenylthio), aryl (e.g., phenyl, tolyl, alkyloxyphenyl, alkyloxycarbonylphenyl, halophenyl), heterocyclyl, heteroaryl, amino (e.g., amino, mono- and di- C<sub>1</sub>-C<sub>3</sub> alkanylamino, methylphenylamino, methylbenzylamino, C<sub>1</sub>-C<sub>3</sub> alkanylamido, carbamamido, ureido, guanidino).

"Aromatic ring" is an aromatic hydrocarbon ring system. Aromatic rings are monocyclic or fused bicyclic ring systems. Monocyclic aromatic rings contain from about 5 to about 10 carbon atoms, preferably from 5 to 7 carbon atoms, and most preferably from 5 to 6 carbon atoms in the ring. Bicyclic aromatic rings contain from 8 to 12 carbon atoms, preferably 9 or 10 carbon atoms in the ring. Aromatic rings may be unsubstituted or substituted with from 1 to 4 substituents on the ring. Preferred aromatic ring substituents include: halo, cyano, alkyl, heteroalkyl, haloalkyl, phenyl, phenoxy or any combination thereof. More preferred substituents include halo and haloalkyl. Preferred aromatic rings include naphthyl and phenyl. The most preferred aromatic ring is phenyl.

"Carbocyclic aliphatic ring" is a saturated or unsaturated hydrocarbon ring. Carbocyclic aliphatic rings are not aromatic. Carbocyclic aliphatic rings are monocyclic, or are fused, spiro, or bridged bicyclic ring systems. Monocyclic carbocyclic aliphatic rings contain from about 4 to about 10 carbon atoms, preferably from 4 to 7 carbon atoms, and most preferably from 5 to 6 carbon atoms in the ring. Bicyclic carbocyclic aliphatic rings contain from 8 to 12 carbon atoms, preferably from 9 to 10 carbon atoms in the ring. Carbocyclic aliphatic rings may be unsubstituted or substituted with from 1 to 4 substituents on the ring. Preferred carbocyclic aliphatic ring substituents include: halo, cyano, alkyl, heteroalkyl, haloalkyl, phenyl, phenoxy or any combination thereof. More preferred substituents include halo and haloalkyl. Preferred carbocyclic aliphatic rings include cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl. More preferred carbocyclic aliphatic rings include cyclohexyl, cycloheptyl, and cyclooctyl. The most preferred carbocyclic aliphatic ring is cycloheptyl.

"Halo" is fluoro, chloro, bromo or iodo. Preferred halo are fluoro, chloro and bromo; more preferred are chloro and fluoro, especially fluoro.

"Haloalkyl" is a straight, branched, or cyclic hydrocarbon substituted with one or more halo substituents. Preferred haloalkyl are C<sub>1</sub>-C<sub>12</sub>; more preferred are C<sub>1</sub>-C<sub>6</sub>; more preferred still are C<sub>1</sub>-C<sub>3</sub>. Preferred halo substituents are fluoro and chloro. The most preferred haloalkyl is trifluoromethyl.

"Heteroalkyl" is a saturated or unsaturated chain containing carbon and at least one heteroatom, wherein no two heteroatoms are adjacent. Heteroalkyl chains contain

from 1 to 18 member atoms (carbon and heteroatoms) in the chain, preferably 1 to 12, more preferably 1 to 6, more preferably still 1 to 4. Heteroalkyl chains may be straight or branched. Preferred branched heteroalkyl have one or two branches, preferably one branch. Preferred heteroalkyl are saturated. Unsaturated heteroalkyl have one or more double bonds and/or one or more triple bonds. Preferred unsaturated heteroalkyl have one or two double bonds or one triple bond, more preferably one double bond. Heteroalkyl chains may be unsubstituted or substituted with from 1 to 4 substituents. Preferred heteroalkyl are unsubstituted. Preferred heteroalkyl substituents include methyl, ethyl, propyl and butyl, halo, hydroxy, alkoxy (e.g., methoxy, ethoxy, propoxy, butoxy, pentoxy), aryloxy (e.g., phenoxy, chlorophenoxy, tolyloxy, methoxyphenoxy, benzyloxy, alkyloxycarbonylphenoxy, acyloxyphenoxy), acyloxy (e.g., propionyloxy, benzoyloxy, acetox), carbamoyloxy, carboxy, mercapto, alkylthio, acylthio, arylthio (e.g., phenylthio, chlorophenylthio, alkylphenylthio, alkoxyphenylthio, benzylthio, alkyloxycarbonylphenylthio), aryl (e.g., phenyl, tolyl, alkyloxyphenyl, alkyloxycarbonylphenyl, halophenyl), heterocyclyl, heteroaryl, amino (e.g., amino, mono- and di- C<sub>1</sub>-C<sub>3</sub> alkylamino, methylphenylamino, methylbenzylamino, C<sub>1</sub>-C<sub>3</sub> alkylamido, carbamamido, ureido, guanidino).

"Heteroatom" is a nitrogen, sulfur, or oxygen atom. Groups containing more than one heteroatom may contain different heteroatoms.

"Heterocyclic aliphatic ring" is a saturated or unsaturated ring containing carbon and from 1 to about 4 heteroatoms in the ring, wherein no two heteroatoms are adjacent in the ring and no carbon in the ring that has a heteroatom attached to it also has a hydroxyl, amino, or thiol group attached to it. Heterocyclic aliphatic rings are not aromatic. Heterocyclic aliphatic rings are monocyclic, or are fused or bridged bicyclic ring systems. Monocyclic heterocyclic aliphatic rings contain from about 4 to about 10 member atoms (carbon and heteroatoms), preferably from 4 to 7, and most preferably from 5 to 6 in the ring. Bicyclic heterocyclic aliphatic rings contain from 8 to 12 member atoms, preferably 9 or 10 in the ring. Heterocyclic aliphatic rings may be unsubstituted or substituted with from 1 to 4 substituents on the ring. Preferred heterocyclic aliphatic ring substituents include: halo, cyano, alkyl, heteroalkyl, haloalkyl, phenyl, phenoxy or any combination thereof. More preferred substituents include halo and haloalkyl. Preferred heterocyclic aliphatic rings include piperzyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl and piperdyl.

"Heteroaromatic ring" is an aromatic ring system containing carbon and from 1 to about 4 heteroatoms in the ring. Heteroaromatic rings are monocyclic or fused bicyclic ring systems. Monocyclic heteroaromatic rings contain from about 5 to about 10

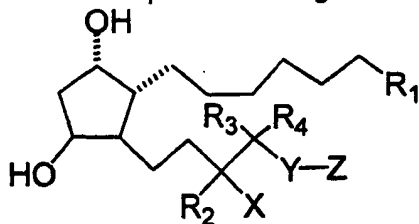
member atoms (carbon and heteroatoms), preferably from 5 to 7, and most preferably from 5 to 6 in the ring. Bicyclic heteroaromatic rings contain from 8 to 12 member atoms, preferably 9 or 10 in the ring. Heteroaromatic rings may be unsubstituted or substituted with from 1 to 4 substituents on the ring. Preferred heteroaromatic ring substituents include: halo, cyano, alkyl, heteroalkyl, haloalkyl, phenyl, phenoxy or any combination thereof. More preferred substituents include halo, haloalkyl, and phenyl. Preferred heteroaromatic rings include thienyl, thiazolo, purinyl, pyrimidyl, pyridyl, and furanyl. More preferred heteroaromatic rings include thienyl, furanyl, and pyridyl. The most preferred heteroaromatic ring is thienyl.

"Lower alkyl" is an alkyl chain radical comprised of 1 to 6, preferably 1 to 4 carbon atoms.

"Phenyl" is a monocyclic aromatic ring which may or may not be substituted with from about 1 to about 4 substituents. The substituents may be substituted at the *ortho*, *meta* or *para* position on the phenyl ring, or any combination thereof. Preferred phenyl substituents include: halo, cyano, alkyl, heteroalkyl, haloalkyl, phenyl, phenoxy or any combination thereof. More preferred substituents on the phenyl ring include halo and haloalkyl. The most preferred substituent is halo. The preferred substitution pattern on the phenyl ring is *ortho* or *meta*. The most preferred substitution pattern on the phenyl ring is *ortho*.

### Compounds

The subject invention involves compounds having the following structure:



In the above structure,  $R_1$  is  $\text{CO}_2\text{H}$ ,  $\text{C}(\text{O})\text{NHOH}$ ,  $\text{CO}_2\text{R}_5$ ,  $\text{CH}_2\text{OH}$ ,  $\text{S}(\text{O})_2\text{R}_5$ ,  $\text{C}(\text{O})\text{NHR}_5$ ,  $\text{C}(\text{O})\text{NHS}(\text{O})_2\text{R}_5$ , or tetrazole; wherein  $R_5$  is alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring. Preferred  $R_5$  is  $\text{CH}_3$ ,  $\text{C}_2\text{H}_5$ ,  $\text{C}_3\text{H}_7$ . Preferred  $R_1$  is  $\text{CO}_2\text{H}$ ,  $\text{C}(\text{O})\text{NHOH}$ ,  $\text{CO}_2\text{CH}_3$ ,  $\text{CO}_2\text{C}_2\text{H}_5$ ,  $\text{CO}_2\text{C}_3\text{H}_7$ ,  $\text{CO}_2\text{C}_4\text{H}_9$ ,  $\text{CO}_2\text{C}_3\text{H}_7\text{O}_2$ , and  $\text{C}(\text{O})\text{NHS}(\text{O})_2\text{R}_5$ . More preferred  $R_1$  is  $\text{CO}_2\text{H}$ ,  $\text{C}(\text{O})\text{NHOH}$ ,  $\text{CO}_2\text{CH}_3$ , and  $\text{CO}_2\text{C}_3\text{H}_5$ . Most preferred  $R_1$  is  $\text{CO}_2\text{H}$  and  $\text{CO}_2\text{CH}_3$ .

In the above structure,  $R_2$  is H or lower alkyl. Preferred  $R_2$  is H and  $\text{CH}_3$ . Most preferred  $R_2$  is H.



In the above structure, X is  $\text{NR}_6\text{R}_7$ ,  $\text{OR}_8$ ,  $\text{SR}_9$ ,  $\text{S(O)R}_9$ ,  $\text{S(O)}_2\text{R}_9$ , or F; wherein  $\text{R}_6$ ,  $\text{R}_7$ , and  $\text{R}_8$  are independently selected from the group consisting of H, acyl, alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, and heteroaromatic ring; and wherein  $\text{R}_9$  is alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring. Preferred  $\text{R}_6$  and  $\text{R}_7$  are H,  $\text{CH}_3$  and  $\text{C}_2\text{H}_5$ . Preferred  $\text{R}_8$  is H,  $\text{CH}_3$ ,  $\text{C}_2\text{H}_5$ , and  $\text{C}_3\text{H}_7$ . Preferred  $\text{R}_9$  is  $\text{CH}_3$  and  $\text{C}_2\text{H}_5$ . Preferred X is  $\text{NR}_6\text{R}_7$  and  $\text{OR}_8$ . Most preferred X is OH.

In the above structure,  $\text{R}_3$  and  $\text{R}_4$  are independently H,  $\text{CH}_3$ ,  $\text{C}_2\text{H}_5$ ,  $\text{OR}_{10}$ ,  $\text{SR}_{10}$ , or OH, except that both  $\text{R}_3$  and  $\text{R}_4$  are not OH; wherein  $\text{R}_{10}$  is alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring,  $\text{R}_{10}$  having from 1 to about 8 member atoms. Preferred  $\text{R}_3$  and  $\text{R}_4$  are H.

In the above structure, Y is  $(\text{CH}_2)_n$ ; n being an integer from 0 to about 3. Preferred n is 0, 1, and 2. Most preferred n is 1.

In the above structure, Z is carbocyclic aliphatic ring, heterocyclic aliphatic ring, monocyclic heteroaromatic ring, or substituted phenyl when n is 0, 2, or 3; and Z is carbocyclic aliphatic ring, heterocyclic aliphatic ring, or substituted phenyl when n is 1. Preferred Z is monocyclic. More preferred Z is substituted phenyl and monocyclic heteroaromatic ring. The most preferred Z is substituted phenyl and substituted or unsubstituted thienyl.

The invention also includes optical isomers, diastereomers and enantiomers of the above structure. Thus, at all stereocenters where stereochemistry is not defined ( $\text{C}_{11}$ ,  $\text{C}_{12}$ ,  $\text{C}_{15}$ , and  $\text{C}_{16}$ ), both epimers are envisioned. Preferred stereochemistry at all such stereocenters of the compounds of the invention mimic that of naturally occurring  $\text{PGF}_{2a}$ .

It has been discovered that the novel PGF analogs of the subject invention are useful for treating bone disorders, especially those that require a significant increase in bone mass, bone volume, or bone strength. Surprisingly, the compounds of the subject invention have been found to provide the following advantages over known bone disorder therapies: (1) An increase trabecular number through formation of new trabeculae; (2) An increase in bone mass and bone volume while maintaining a more normal bone turnover rate; and (3) An increase in bone formation at the endosteal surface without increasing cortical porosity.

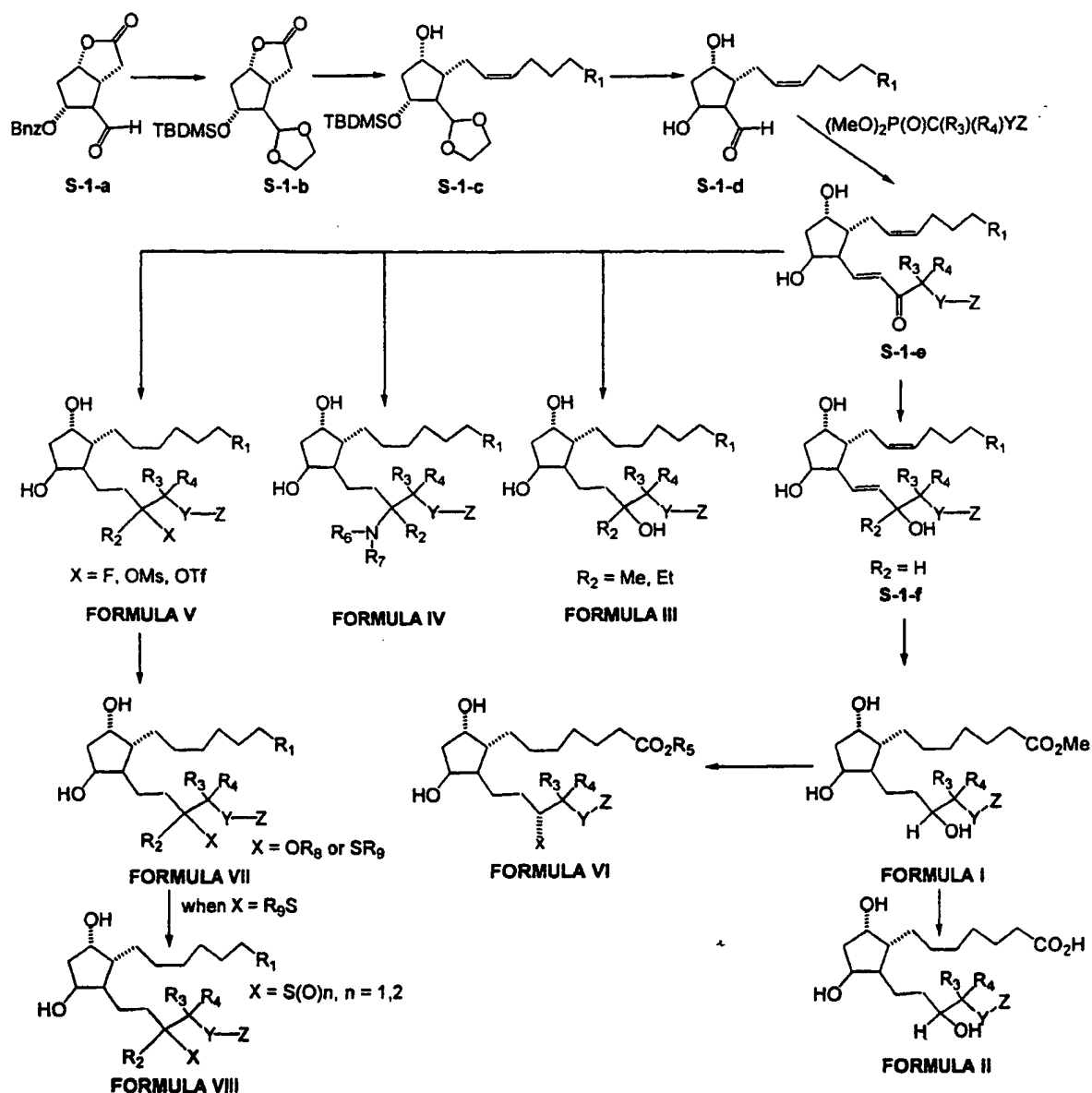
In order to determine and assess pharmacological activity, testing of the subject compounds in animals is carried out using various assays known to those skilled in the art. For example, the bone activity of the subject compounds can be conveniently demonstrated using an assay designed to test the ability of the subject compounds to

increase bone volume, mass, or density. An example of such assays is the ovariectomized rat assay.

In the ovariectomized rat assay, six-month old rats are ovariectomized, aged 2 months, and then dosed once a day subcutaneously with a test compound. Upon completion of the study, bone mass and/or density can be measured by dual energy x-ray absorptometry (DXA) or peripheral quantitative computed tomography (pQCT), or micro computed tomography (mCT). Alternatively, static and dynamic histomorphometry can be used to measure the increase in bone volume or formation.

Pharmacological activity for glaucoma can be demonstrated using assays designed to test the ability of the subject compounds to decrease intraocular pressure. Examples of such assays are described in the following reference, incorporated herein: C. Liljebris, G. Selen, B. Resul, J. Sternschantz, and U. Hacksell, "Derivatives of 17-Phenyl-18,19,20-trinorprostaglandin F<sub>2</sub> $\alpha$  Isopropyl Ester: Potential Antiglaucoma Agents", Journal of Medicinal Chemistry, Vol. 38 No. 2 (1995), pp. 289-304.

Compounds useful in the subject invention can be made using conventional organic syntheses. A particularly preferred synthesis is the following general reaction scheme:



Compounds depicted by **S1f** are available from compounds of the type depicted by **S1e** via standard reduction reactions. Compounds depicted by **Formula I** are available from compounds of **S1f** via simultaneous saturation of the double bonds of **S1f**. Compounds depicted by **Formula I** are exemplified in Examples 2, 4, 5, 7, 9, 11, 13, 16, 18, 20, 22, 24, 26, and 28. Compounds depicted by **Formula II** are prepared through a

simple deesterification protocol of the compounds of **Formula I**. Compounds depicted by **Formula II** are exemplified in Examples 1, 3, 6, 8, 10, 12, 14, 15, 17, 19, 21, 23, 25, 27, and 29. Compounds depicted by **Formula III** can be prepared from compounds such of **S1e** via the addition of a carbon nucleophile followed by saturation and saponification. Compounds depicted by **Formula III** are exemplified in Examples 43 and 44. Compounds depicted by **Formula IV** can be prepared via imine formation followed by imine reduction, *N*-alkylation, hydrogenation, and saponification. Additional compounds depicted by **Formula IV** can be prepared via imine formation, as previously mentioned, followed by nucleophilic addition to the resulting imine followed by double bond saturation and saponification. Compounds depicted by **Formula IV** are exemplified in Examples 48, 49, and 50.

Compounds depicted by **Formula V** and **Formula VII** can be prepared through dihydroxyl protection of compounds of **S1e** followed by standard nucleophilic reduction of the ketone. The resulting free alcohol can be activated and displaced with nucleophiles such as, but not limited to, fluoride, alkoxide or sulfide to give compounds depicted by **Formula V** or **Formula VII**. Compounds depicted by **Formula V** are exemplified in Examples 36, 37, and 38. Compounds depicted by **Formula VII** are exemplified in Examples 39, 40, 41, 42, and 45. Compounds depicted by **Formula VIII** are prepared by the selective oxidation of compounds of **Formula VII** with the proviso that X must be sulfur. Compounds depicted by **Formula VIII** are exemplified in Examples 46 and 47. Compounds of the type depicted by **Formula VI** can be prepared from either compounds of **Formula I** or **Formula II** (compounds depicted by **Formula II** may require carboxylate activation) through nucleophilic addition to an activated carboxylate to produce an amide or new ester linkage to give the resulting hydroxamic acid, sulfonamide, or ester. Compounds depicted by **Formula VI** are exemplified in Examples 30 - 35.

The following non-limiting examples illustrate the compounds, compositions, and uses of the present invention.

### Examples

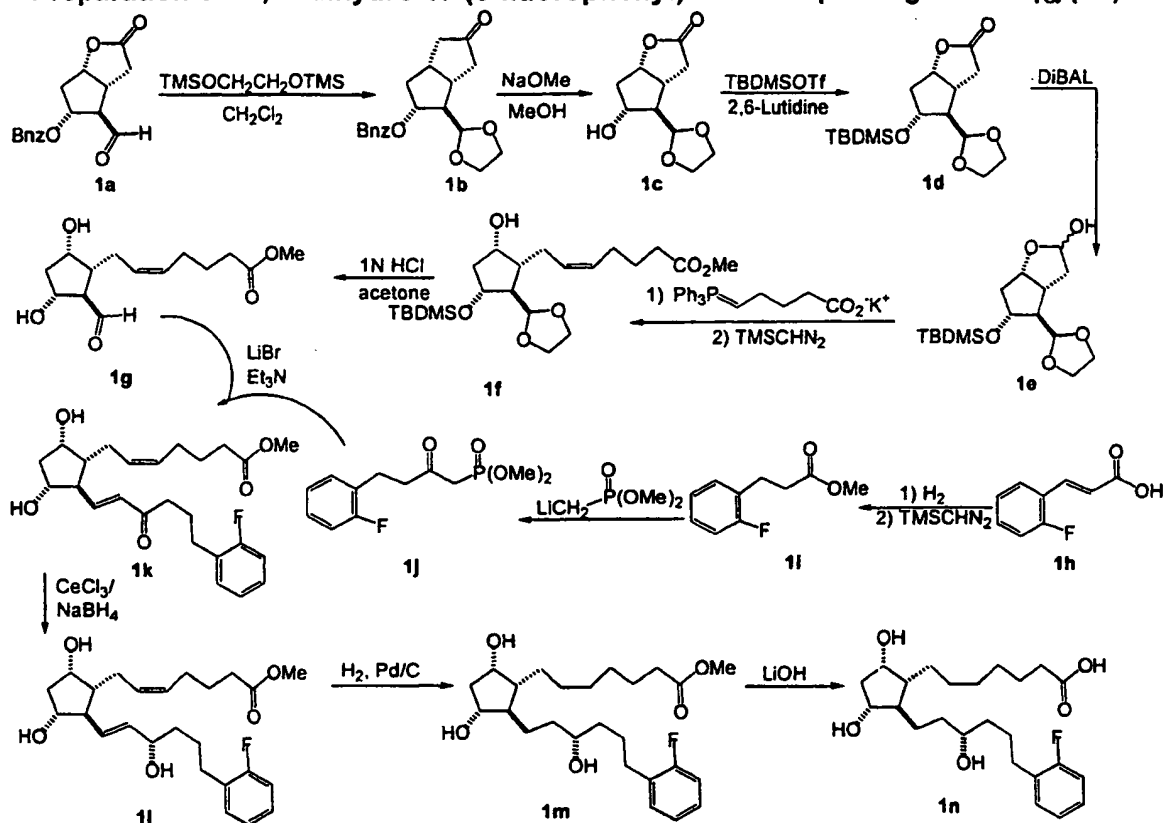
Compounds are analyzed using  $^1\text{H}$  and  $^{13}\text{C}$  NMR, Elemental analysis, mass spectra, high resolution mass spectra and/or IR spectra as appropriate.

Typically, inert solvents are used, preferably in dried form. For example, tetrahydrofuran (THF) is distilled from sodium and benzophenone, diisopropylamine is distilled from calcium hydride and all other solvents are purchased as the appropriate grade. Chromatography is performed on silica gel (70-230 mesh; Aldrich) or (230-400 mesh; Merck) as appropriate. Thin layer chromatography analysis is performed on glass

mounted silica gel plates (200-300 mesh; Baker) and visualized using UV, 5% phosphomolybdic acid in EtOH, potassium permanganate in water, iodine, *p*-anisaldehyde in ethanol, or ammonium molybdate/ceric sulfate in 10% aqueous H<sub>2</sub>SO<sub>4</sub>.

### Example 1

#### Preparation of 13,14-dihydro-17-(3-fluorophenyl)-17-trinor-prostaglandin F<sub>1α</sub> (1n):



a. **7-benzoyloxy-6-(2,5-dioxolanyl)-2-oxabicyclo[3.3.0]octan-3-one (1b):** In a round-bottomed flask equipped with a magnetic stir bar is placed 1,2-bis(trimethylsilyloxy)ethane (1.3 equiv.) in methylene chloride containing trimethylsilyltrifluoromethanesulfonate (1 mL) at -78°C. To this is added, within 20 minutes, a solution of 1a (1 equiv) in CH<sub>2</sub>Cl<sub>2</sub>. The reaction is stirred for 1 hour at -78°C and then slowly warmed to 25°C for 1 hour. The reaction is quenched at 0°C with water, extracted with CH<sub>2</sub>Cl<sub>2</sub>, dried over MgSO<sub>4</sub>, and concentrated *in vacuo* to give crude 1b.

b. **6-(2,5-dioxolanyl)-7-hydroxy-2-oxabicyclo[3.3.0]octan-3-one (1c):** To a well stirred solution of crude 1b (1 equiv) in methanol at 0°C is added a suspension of sodium methoxide (1.2 equiv) in MeOH. The reaction stirred at 0°C for 1 hour and then warmed to 25°C for 1 hour. The reaction is neutralized with acidic ion exchange resin which is washed thoroughly with MeOH. The filtrate is concentrated *in vacuo* to give a syrup which

is subjected to flash chromatography on silica gel eluting with 4:1 hexane : ethyl acetate and 2% MeOH in CH<sub>2</sub>Cl<sub>2</sub> to give **1c** as a yellow syrup.

c. **6-(2,5 dioxolanyl)-2-oxa-7-(1,1,2,2-tetramethyl-1-silapropoxy) bicyclo [3.3.0] octan-3-one (1d)**: In a round-bottomed flask with a magnetic stir bar, is stirred a solution of **1c** (1 equiv) in CH<sub>2</sub>Cl<sub>2</sub>. To this solution is added dropwise at -78°C 2,6-lutidine (1.9 equiv) followed by TBDMSOTf (1.8 eq). The reaction stirred for 30 minutes at -78°C and then warmed to 25°C overnight. The reaction is quenched with water. The organic layer is washed with water, dried over MgSO<sub>4</sub>, and concentrated *in vacuo* to give a yellow oil which is subjected to flash chromatography on silica gel eluting with hexanes then 1% MeOH in CH<sub>2</sub>Cl<sub>2</sub>. The product is then washed with 1N HCl, 0.1N HCl, water, and brine to give **1d**.

d. **6-(2,5 dioxolanyl)-2-oxa-7-(1,1,2,2-tetramethyl-1-silapropoxy) bicyclo [3.3.0] octan-2-ol (1e)**: In a round-bottomed flask with a magnetic stir bar, is stirred a solution of **1d** (1 equiv) in dry toluene. To this solution, at -78°C, is slowly added DIBAL (1.24 equiv). The reaction mixture is stirred for 2 hours and then warmed to 0°C. Saturated NH<sub>4</sub>Cl is added to the reaction mixture which is then slowly warmed to 25°C. Diluted with water, the insoluble precipitate is removed by suction filtration and the solid is washed with EtOAc. The liquid phase is extracted with EtOAc and the combined organic phase is dried over MgSO<sub>4</sub> and concentrated *in vacuo* to give a yellow syrup. The product, **1e**, must either be used immediately or stored at -70°C overnight.

e. **methyl 7-(5-(2,5-dioxolanyl)-2-hydroxy-4-(1,1,2,2-tetramethyl-1-silapropoxy) cyclopentyl)hept-5-enoate (1f)**: To a suspension of (4-carboxybutyl)triphenylphosphonium bromide (2.2 equiv) in THF at 0°C under N<sub>2</sub> is added dropwise a solution of KHMDS (4.4 equiv). The resulting deep orange color reaction mixture is stirred for 1 hour at 25°C. To the reaction mixture above at -78°C is added a solution of **1e** (1 equiv) in THF. The reaction mixture is allowed to warm to 25°C overnight. The reaction is quenched with water at 0°C and the pH is adjusted to 3.5 - 4.0 with 1N HCl. The water phase is extracted with EtOAc and the combined organic phase is dried over MgSO<sub>4</sub> and is concentrated *in vacuo* to give a reddish-brown syrup containing crude acid. To a well stirred solution of crude acid in ether and MeOH at 0°C is added TMS-diazomethane until a yellow color persists. The addition of 1 drop of glacial acetic acid, and thin layer chromatography verifies the reaction has gone to completion. The reaction solution is concentrated *in vacuo* and purified via flash chromatography on silica gel eluting with 30% EtOAc in hexanes yielding **1f**.

f. **methyl 7-(2,4-dihydroxy-5-formyl-cyclopentyl)hept-5-enoate (1g)**: In a round-bottomed flask with a magnetic stir bar is placed an amount of the ketal, **1f**. To this flask is

added a sufficient amount of a mixture of 2 parts acetone to 1 part 1N HCl to bring the ketal completely into solution. This material is stirred until, by TLC, the starting material is consumed, typically overnight. The crude mixture, containing the product **1g**, is extracted with ether, and the ether extract re-esterified *in situ* with, preferably, TMS-diazomethane. The organic extracts were concentrated under reduced pressure at 0°C and used immediately without further purification.

**g. Methyl 3-(2-fluorophenyl)propionate (1i):** In a Parr vessel is placed 2-fluorocinnamic acid (**1h**) (1.0 equiv) and palladium on carbon in a 1/1 methanol/ethyl acetate solution. The heterogeneous solution is placed on a Parr shaker and treated with hydrogen (50 psi) until uptake has ceased. The mixture is filtered through Celite and concentrated under reduced pressure. The residue is taken up in diethyl ether and treated with diazomethane until a yellow color persists. The solution is concentrated under reduced pressure to give the crude methyl ester. Purification is effected by column chromatography on silica gel (hexane/ethyl acetate 5/1) to yield Methyl 3-(2-fluorophenyl)propionate (**1i**) in quantitative yield.

**h. Dimethyl-4-(2-fluorophenyl)-2-oxo-butylphosphonate (1j):** In a flame-dried, round-bottomed flask equipped with a stir bar and thermometer is placed dimethylmethyl phosphonate (1.0 equiv.) in anhydrous THF. The solution is cooled to -78°C and treated with *n*-butyllithium (1.05 equiv.). The reaction mixture is allowed to stir for 15 minutes. To this solution is added methyl-3-(2-fluorophenyl)propionate (1.1 equiv.) in anhydrous THF. The mixture is allowed to warm to room temperature over the next 6 hours. The mixture is treated with a saturated solution of ammonium chloride and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer is washed with water followed by brine. The combined aqueous layers are back extracted with CH<sub>2</sub>Cl<sub>2</sub> and the organic layers combined, dried over anhydrous MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. Purification is effected by silica gel column chromatography (hexane/ethyl acetate/ 2-propanol 45/50/5 to hexane/ethyl acetate/2-propanol 40/50/10) to yield 1.34 g (70%) of dimethyl-4-(2-fluorophenyl)-2-oxo-butylphosphonate (**1j**) as an oil.

**i. 17-(2-fluorophenyl)-17-trinor-15-oxo-prostaglandin F<sub>2a</sub> methyl ester (1k):** In a flame-dried, round-bottomed flask equipped with a magnetic stirbar is placed dimethyl-4-(2-fluorophenyl)-2-oxo-butylphosphonate (**1j**) (1.43 equiv) in DME and water. To this solution is added lithium bromide (1.65 equiv), triethylamine (1.65 equiv), and methyl 7-(2-formyl-3,5-dihydroxycyclopentyl)hept-5-enoate (**1g**) (1.0 equiv). The solution is stirred at room temperature for 48 hours. At this point additional triethylamine and water is added and the solution is stirred for an additional hour. The solution is poured into brine and extracted with 3 portions of ethyl acetate. The organic layers are combined, dried over anhydrous

MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. Purification is effected by silica gel column chromatography (dichloromethane/methanol 19/1) to give 17-(2-fluorophenyl)-17-trinor-15-oxo-prostaglandin F<sub>2a</sub> methyl ester (1k) as an oil.

j. **15-(R,S)-17-(2-fluorophenyl)-17-trinor-prostaglandin F<sub>2a</sub> methyl ester (1l):** In a flame-dried round-bottomed flask equipped with a stir bar is placed 17-(2-fluorophenyl)-17-trinor-15-oxo-prostaglandin F<sub>2a</sub> methyl ester (1k) (1.0 equiv), cerium trichloride (1.05 equiv) in methanol. The solution is stirred at room temperature for 5 minutes. The solution is cooled to -10°C and sodium borohydride (1.02 equiv.) in methanol is added. The solution is stirred at -10°C for 3 hours. The mixture is treated with water and the pH brought to 6-7 with 1N hydrochloric acid. The mixture is extracted twice with ethyl acetate, and the organic layers combined, dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification was effected by silica gel column chromatography (3% methanol in dichloromethane to 5% methanol in dichloromethane) to give (43%) of the 15 (R) epimer and (19.6%) of the 15 (S) epimer as colorless oils.

k. **13,14-dihydro-17-(2-fluorophenyl)-17-trinor-prostaglandin F<sub>1α</sub> methyl ester (1m):** In a flame-dried round-bottomed flask equipped with a stir bar was placed 17-(2-fluorophenyl)-17-trinor-prostaglandin F<sub>2a</sub> methyl ester (1l) (1.0 equiv.) and palladium on carbon in ethyl acetate (3 mL). The heterogeneous mixture is treated with hydrogen via a balloon for 18 hours. The mixture is filtered through Celite and concentrated under reduced pressure to give a quantitative yield 13,14-dihydro-17-(2-fluorophenyl)-17-trinor-prostaglandin F<sub>1α</sub> methyl ester (1m).

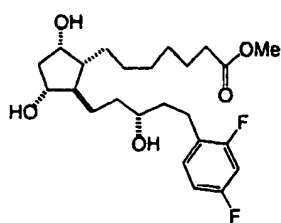
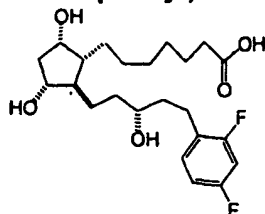
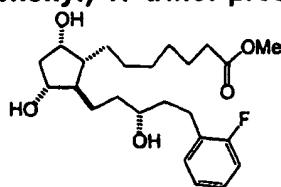
l. **13,14-dihydro-17-(2-fluorophenyl)-17-trinor-prostaglandin F<sub>1α</sub> methyl ester (1n):** In a round-bottomed flask equipped with a stir bar is placed 13,14-dihydro-17-(2-fluorophenyl)-17-trinor-prostaglandin F<sub>1α</sub> methyl ester (1m) (1.0 equiv) and lithium hydroxide monohydrate (1.8 equiv) in a 50/50 THF water solution. The mixture is stirred at room temperature for 6 hours and then diluted with water and acidified to pH 2-3 with 1N HCl. The aqueous phase is extracted 3 times with ethyl acetate and the organic layers combined. The combined organics were dried over anhydrous MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure to yield the crude acid. Purification was effected by HPLC to yield (41%) of an analytical sample. Utilizing substantially the method of Example 1 (and using the appropriate starting materials), the following subject compounds of Examples 2-29 are obtained.

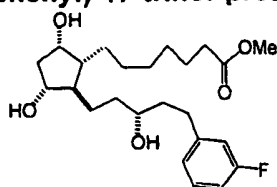
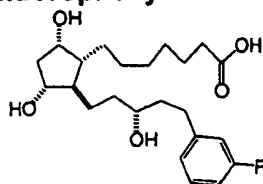
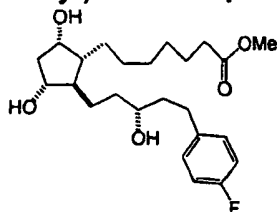
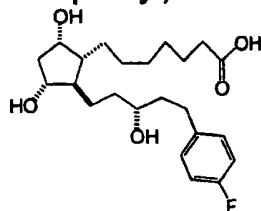
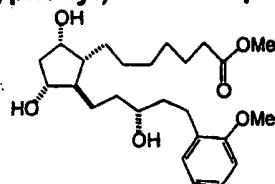
### Example 2

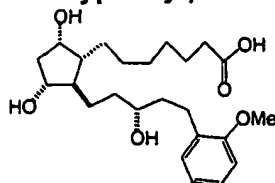
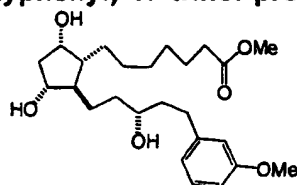
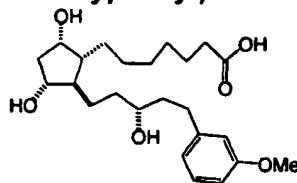
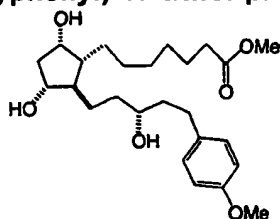
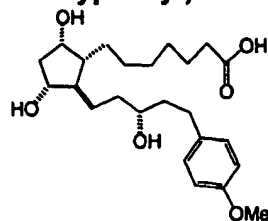
**13,14-dihydro-17-(2,4 difluorophenyl)-17-trinor prostaglandin F<sub>1α</sub> methyl ester**



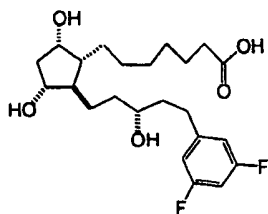
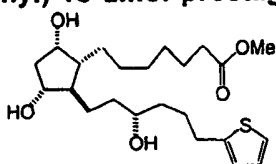
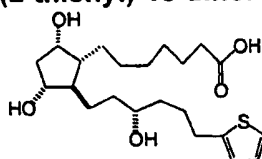
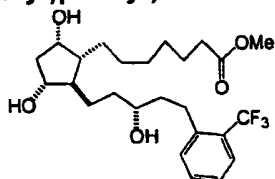
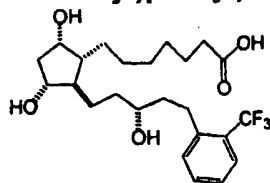
15

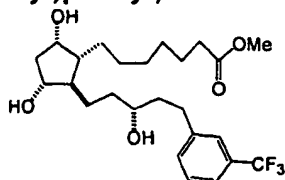
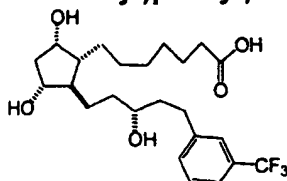
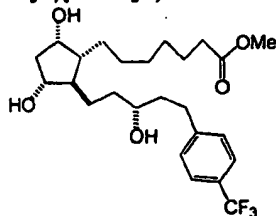
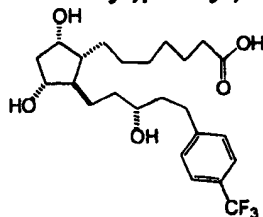
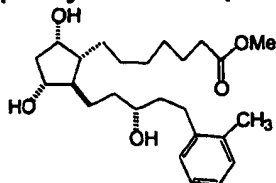
**Example 3****13,14-dihydro-17-(2,4 difluorophenyl)-17-trinor prostaglandin F<sub>1α</sub>****Example 4****13,14-dihydro-17-(2-fluorophenyl)-17-trinor prostaglandin F<sub>1α</sub> methyl ester**

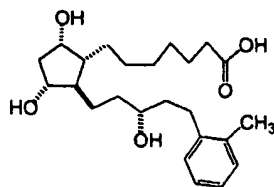
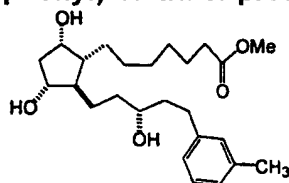
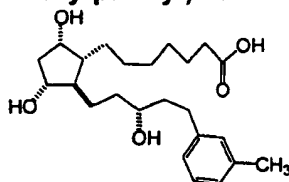
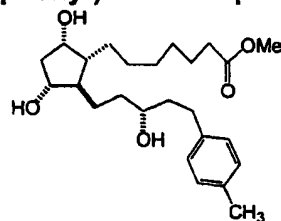
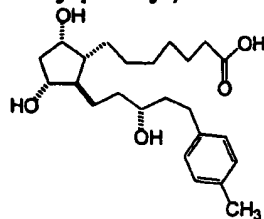
**Example 5****13,14-dihydro-17-(3-fluorophenyl)-17-trinor prostaglandin F<sub>1α</sub> methyl ester****Example 6****13,14-dihydro-17-(3-fluorophenyl)-17-trinor prostaglandin F<sub>1α</sub>****Example 7****13,14-dihydro-17-(4-fluorophenyl)-17-trinor prostaglandin F<sub>1α</sub> methyl ester****Example 8****13,14-dihydro-17-(4-fluorophenyl)-17-trinor prostaglandin F<sub>1α</sub>****Example 9****13,14-dihydro-17-(2-methoxyphenyl)-17-trinor prostaglandin F<sub>1α</sub> methyl ester**

**Example 10****13,14-dihydro-17-(2-methoxyphenyl)-17-trinor prostaglandin F<sub>1α</sub>****Example 11****13,14-dihydro-17-(3-methoxyphenyl)-17-trinor prostaglandin F<sub>1α</sub> methyl ester****Example 12****13,14-dihydro-17-(3-methoxyphenyl)-17-trinor prostaglandin F<sub>1α</sub>****Example 13****13,14-dihydro-17-(4-methoxyphenyl)-17-trinor prostaglandin F<sub>1α</sub> methyl ester****Example 14****13,14-dihydro-17-(4-methoxyphenyl)-17-trinor prostaglandin F<sub>1α</sub>****Example 15****13,14-dihydro-17-(3,5-difluorophenyl)-17-trinor prostaglandin F<sub>1α</sub>**

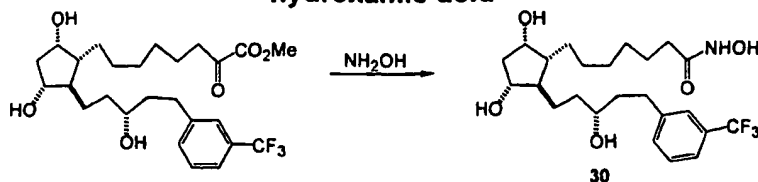
18

**Example 16****13,14-dihydro-18-(2-thienyl)-18-dinor prostaglandin F<sub>1α</sub> methyl ester****Example 17****13,14-dihydro-18-(2-thienyl)-18-dinor prostaglandin F<sub>1α</sub>****Example 18****13,14-dihydro-17-((2-trifluoromethyl)phenyl)-17-trinor prostaglandin F<sub>1α</sub> methyl ester****Example 19****13,14-dihydro-17-((2-trifluoromethyl)phenyl)-17-trinor prostaglandin F<sub>1α</sub>**

**Example 20****13,14-dihydro-17-((3-trifluoromethyl)phenyl)-17-trinor prostaglandin F<sub>1α</sub> methyl ester****Example 21****13,14-dihydro-17-((3-trifluoromethyl)phenyl)-17-trinor prostaglandin F<sub>1α</sub>****Example 22****13,14-dihydro-17-((4-trifluoromethyl)phenyl)-17-trinor prostaglandin F<sub>1α</sub> methyl ester****Example 23****13,14-dihydro-17-((4-trifluoromethyl)phenyl)-17-trinor prostaglandin F<sub>1α</sub>****Example 24****13,14-dihydro-17-(2-methylphenyl)-17-trinor prostaglandin F<sub>1α</sub> methyl ester****Example 25****13,14-dihydro-17-(2-methylphenyl)-17-trinor prostaglandin F<sub>1α</sub>**

**Example 26****13,14-dihydro-17-(3-methylphenyl)-17-trinor prostaglandin F<sub>1α</sub> methyl ester****Example 27****13,14-dihydro-17-(3-methylphenyl)-17-trinor prostaglandin F<sub>1α</sub>****Example 28****13,14-dihydro-17-(4-methylphenyl)-17-trinor prostaglandin F<sub>1α</sub> methyl ester****Example 29****13,14-dihydro-17-(4-methylphenyl)-17-trinor prostaglandin F<sub>1α</sub>**

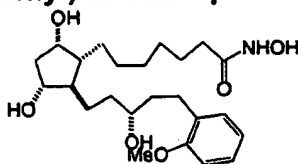
**Example 30**  
**13,14-dihydro-17-((3-trifluoromethyl)phenyl)-17-trinor prostaglandin F<sub>1α</sub>-1-hydroxamic acid**



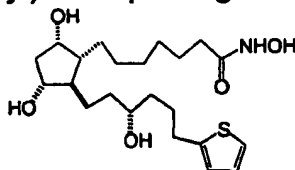
To a solution of 13,14-dihydro-17-(3-trifluoromethyl)-phenyl trinor prostaglandin F<sub>1α</sub> methyl ester (Example 20) in methanol is added hydroxylamine in basic methanol (1.25 equiv.). The solution is stirred at room temperature for 18 hours. The solution is treated with 1N hydrochloric acid and extracted with ethyl acetate. The organic layer is washed with brine and dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue is purified by HPLC to yield 13,14-dihydro-17-((3-trifluoromethyl)phenyl)-17-trinor prostaglandin F<sub>1α</sub>-1-hydroxamic acid.

Utilizing substantially the method of Example 30 (and using the appropriate ester), the following subject compounds of Examples 31 and 32 are obtained.

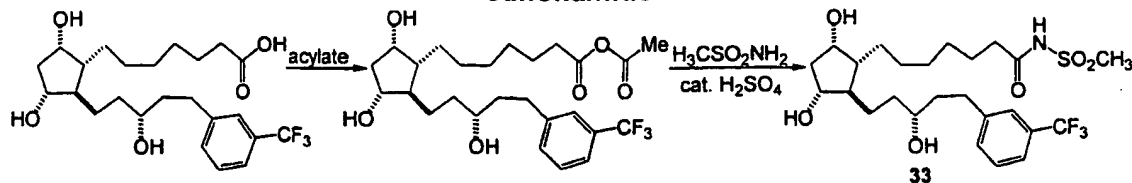
**Example 31**  
**13,14-dihydro-17-(2-methoxyphenyl)-17-trinor prostaglandin F<sub>1α</sub>-1-hydroxamic acid**



**Example 32**  
**13,14-dihydro-18-(2-thienyl)-dinor prostaglandin F<sub>1α</sub>-1-hydroxamic acid**



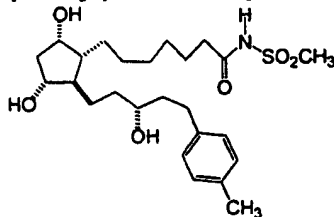
**Example 33**  
**13,14-dihydro-17-((4-trifluoromethyl)phenyl)-17-trinor prostaglandin F<sub>1α</sub>-1-sulfonamide**



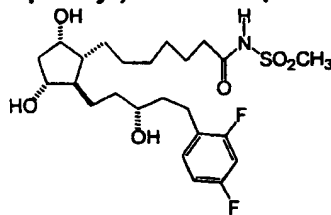
Example 23 is converted to the anhydride followed by treatment with methanesulfonylamine as disclosed in A.D. Kemp and H. Stephen, J. Chem. Soc. (1948) p. 110.

Utilizing substantially the method of Example 33 (and using the appropriate acid), the following subject compounds of Examples 34 and 35 are obtained.

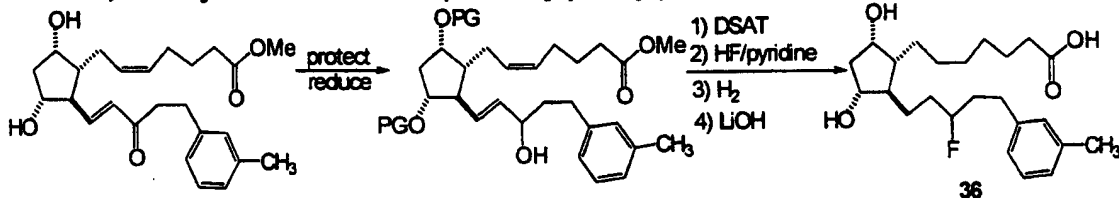
**Example 34**  
**13,14-dihydro-17-(4-methylphenyl)-17-trinor prostaglandin F<sub>1α</sub>-1-sulfonamide**



**Example 35**  
**13,14-dihydro-17-(2,4 difluorophenyl)-17-trinor prostaglandin F<sub>1α</sub>-1-sulfonamide**



**Example 36**  
**13,14-dihydro-15-fluoro-17-(3-methylphenyl)-17-trinor prostaglandin F<sub>1α</sub>**



The precursor to Example 27 corresponding to 1k from Example 1 is protected and reduced to give the 9,11-protected bis ether. The resulting compound is treated with diethylaminosulfur trifluoride (DSAT) (as disclosed in the following references: Org. React. Vol. 35 (1988) p. 513; J. Org. Chem. Vol. 40 (1975) p. 574; and references cited therein) to

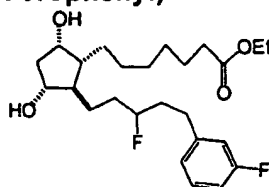


give 13,14-dihydro-15-fluoro-17-(3-methylphenyl)-17-trinor prostaglandin  $F_{1\alpha}$  after the appropriate transformation as described in Example 1.

Examples 37 and 38 are prepared in a manner substantially similar to Example 36 using the appropriate intermediate corresponding to 1k (from Example 5 and Example 25 respectively) in Example 1 followed by standard esterification with the appropriate alcohol.

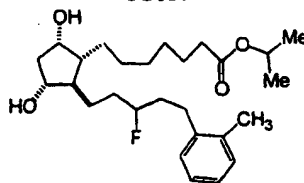
#### Example 37

**13,14-dihydro-15-fluoro-17-(3-fluorophenyl)-17-trinor prostaglandin  $F_{1\alpha}$  ethyl ester**



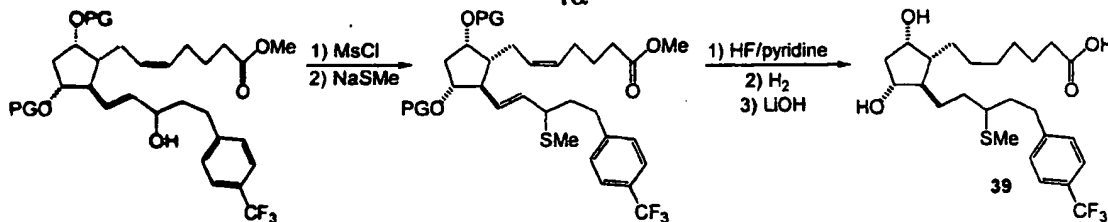
#### Example 38

**13,14-dihydro-15-fluoro-17-(2-methylphenyl)-17-trinor prostaglandin  $F_{1\alpha}$  isopropyl ester**



#### Example 39

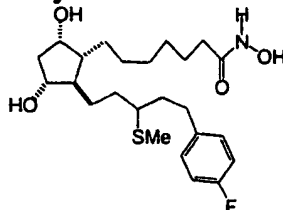
**13,14-dihydro-15-methylthio-17-((4-trifluoromethyl)phenyl)-17-trinor prostaglandin  $F_{1\alpha}$**



The precursor to Example 23 corresponding to 1k from Example 1 is protected and reduced to give the 9,11-protected bis ether. This compound is treated with methanesulfonyl chloride (1.2 equiv) and base (1.2 equiv) (as disclosed in the following references: *J.C.S. Chem. Comm.* (1975) p. 658; *Tetrahedron Lett.* (1975) p. 3183; and references cited therein) to generate the intermediate mesylate, which is then treated immediately with nucleophiles (sodium thiomethoxide) (as disclosed in *Tetrahedron Lett.* Vol. 23 (1982) p. 3463 and references cited therein.) to give the protected thioalkyl ether. Subsequent transformation as described in Example 1 provides 13,14-dihydro-15-methylthio-17-((4-trifluoromethyl)phenyl)-17-trinor prostaglandin  $F_{1\alpha}$ .

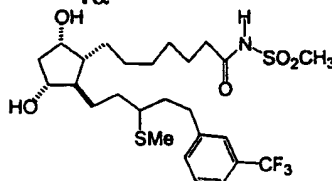
Example 40 is prepared in a manner substantially similar to Example 39 (from a precursor corresponding to 1k from Example 7) followed by conversion to the hydroxamic acid as shown in Example 30.

**Example 40**  
**13,14-dihydro-15-methylthio-17-(4-fluorophenyl)-17-trinor prostaglandin F<sub>1α</sub> hydroxamic acid**

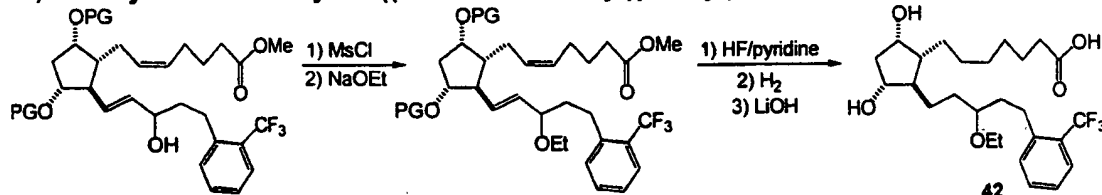


Example 41 is prepared in a substantially similar manner as Example 39 (from a precursor corresponding to 1k from Example 21) followed by conversion to the sulfonamide as shown in Example 33.

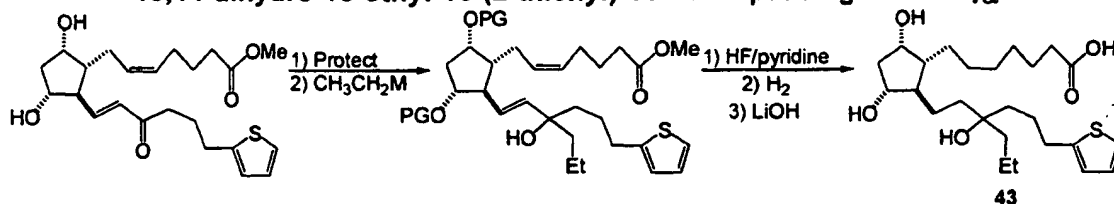
**Example 41**  
**13,14-dihydro-15-methylthio-17-((3-trifluoromethyl)phenyl)-17-trinor prostaglandin F<sub>1α</sub>-sulfonamide**



**Example 42**  
**13,14-dihydro-15-ethoxy-17-((2-trifluoromethyl)phenyl)-17-trinor prostaglandin F<sub>1α</sub>**

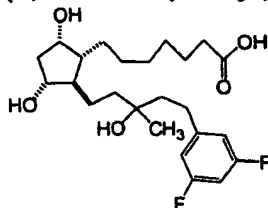


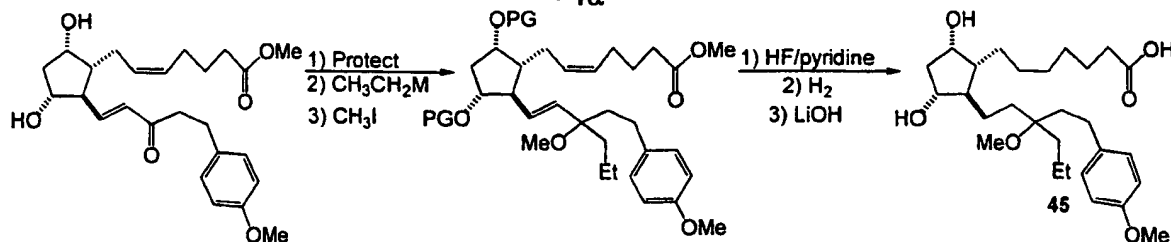
The precursor to Example 19 corresponding to 1k from Example 1 is protected and reduced to give the 9,11-protected bis ether. This compound is treated with methanesulfonyl chloride (1.2 equiv.) and base (1.2 equiv.) (as disclosed in the following references: *J.C.S. Chem. Comm.* (1975) p. 658; *Tetrahedron Lett.* (1975) p. 3183; and references cited therein.) to generate the intermediate mesylate, which is then treated immediately with sodium ethoxide to give the protected alkyl ether. Subsequent transformation as described in Example 1 provides 13,14-dihydro-15-ethoxy-17-((2-trifluoromethyl)phenyl)-17-trinor prostaglandin F<sub>1α</sub>.

**Example 43****13,14-dihydro-15-ethyl-18-(2-thienyl)-18-dinor prostaglandin F<sub>1α</sub>**

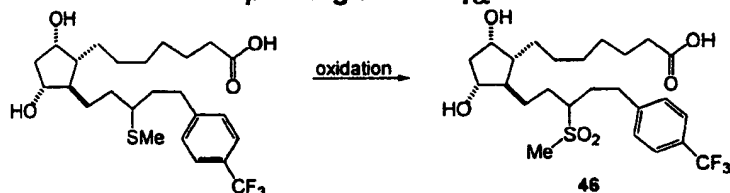
The precursor to Example 17 corresponding to 1k from Example 1 is protected and reduced to give the 9,11-protected bis ether. The resulting protected diol is treated with one of a variety of carbon nucleophiles, such as ethyl magnesium bromide to give the resulting tertiary alcohol. Deprotection followed by the transformation outlined in Example 1 provides 13,14-dihydro-15-ethyl-18-(2-thienyl)-18-dinor prostaglandin F<sub>1α</sub>.

Utilizing substantially the method of Example 43 (and using the appropriate carbon nucleophile), the following subject compound of Example 44 is obtained.

**Example 44****13,14-dihydro-15-methyl-17-(3,5-difluorophenyl)-17-trinor prostaglandin F<sub>1α</sub>**

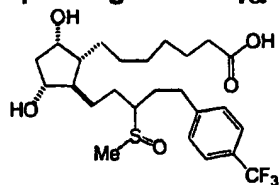
**Example 45****13,14-dihydro-15-ethyl-15-methoxy-17-(4-methoxyphenyl)-17-trinor prostaglandin F<sub>1α</sub>**

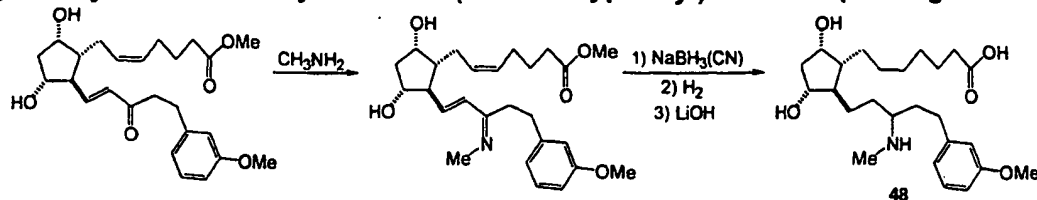
The compound of Example 45 is prepared by utilizing the protocol outlined in Example 43 (from the precursor corresponding to 1k for Example 13) followed by O-alkylation of the resulting C<sub>15</sub> alkoxide with a variety of alkyl halides (iodomethane in this example). This is followed by deprotection, hydrogenation, and saponification as outlined in Example 43 and Example 1 to give 13,14-dihydro-15-ethyl-15-methoxy-17-(4-methoxyphenyl)-17-trinor prostaglandin F<sub>1α</sub>.

**Example 46****13,14-dihydro-15-sulfonylmethyl-17-((4-trifluoromethyl)phenyl)-17-trinor prostaglandin F<sub>1α</sub>**

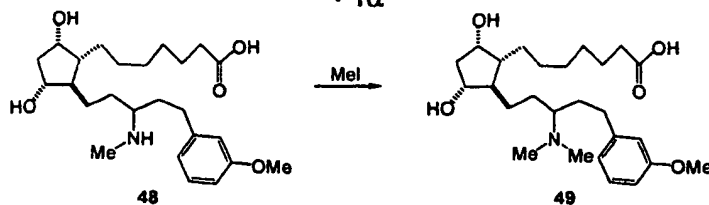
The thiomethyl ether of Example 39 is treated with the appropriate oxidizing agent as disclosed in the following references: *Tetrahedron Lett.* (1982) p. 3467; *Prostaglandins* Vol. 24 (1982) p. 801; *Tetrahedron Lett.* Vol. 23 (1982) p. 1023; and references cited therein.

Utilizing substantially the method of Example 46 (and using the appropriate thioether), the following subject compound of Example 47 is obtained.

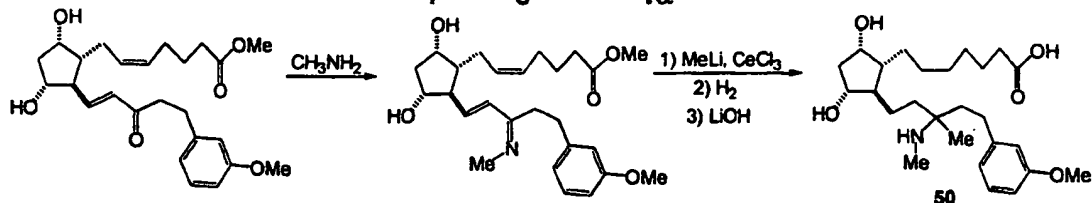
**Example 47****13,14-dihydro-15-sulfoxymethyl-17-((4-trifluoromethyl)phenyl)-17-trinor prostaglandin F<sub>1α</sub>**

**Example 48****13,14-dihydro-15-*N*-methylamino-17-(3-methoxyphenyl)-17-trinor prostaglandin F<sub>1α</sub>**

The intermediate of Example 12 corresponding to 1k is condensed with methylamine followed by reduction with sodium cyanoborohydride to give 13,14-dihydro-15-*N*-methylamino-17-(3-methoxyphenyl)-17-trinor prostaglandin F<sub>1α</sub>, after saponification and deprotection.

**Example 49****13,14-dihydro-15-*N,N'*-dimethylamino-17-(3-methoxyphenyl)-17-trinor prostaglandin F<sub>1α</sub>**

The compound of Example 49 is prepared from the compound of Example 48 by simple alkylation with iodomethane.

**Example 50****13,14-dihydro-15-aminomethyl-15-methyl-17-(3-methoxyphenyl)-17-trinor prostaglandin F<sub>1α</sub>**

The intermediate imine of Example 48 is treated with methylcerium (excess) (for examples of cerium-mediated nucleophilic additions see the following references: J. Org. Chem., Vol. 49 (1984) p. 3904; J. Am. Chem. Soc., Vol. 111 (1989) p. 4392; and references therein) to give 13,14-dihydro-15-aminomethyl-15-methyl-17-(3-methoxyphenyl)-17-trinor prostaglandin F<sub>1α</sub> after hydrogenation and saponification as described in Example 1.

**Compositions**

Compositions of the subject invention comprise a safe and effective amount of the subject compounds, and a pharmaceutically-acceptable carrier. As used herein, "safe and effective amount" means an amount of a compound sufficient to significantly induce a positive modification in the condition to be treated, but low enough to avoid serious side effects (at a reasonable benefit/risk ratio), within the scope of sound medical judgment. A safe and effective amount of a compound will vary with the particular condition being treated, the age and physical condition of the patient being treated, the severity of the condition, the duration of the treatment, the nature of concurrent therapy, the particular pharmaceutically-acceptable carrier utilized, and like factors within the knowledge and expertise of the attending physician.

In addition to the compound, the compositions of the subject invention contain a pharmaceutically-acceptable carrier. The term "pharmaceutically-acceptable carrier", as used herein, means one or more compatible solid or liquid filler diluents or encapsulating substances which are suitable for administration to a subject. The term "compatible", as used herein, means that the components of the composition are capable of being commingled with the compound, and with each other, in a manner such that there is no interaction which would substantially reduce the pharmaceutical efficacy of the composition under ordinary use situations. Pharmaceutically-acceptable carriers must, of course, be of sufficiently high purity and sufficiently low toxicity to render them suitable for administration to the subject being treated.

Some examples of substances which can serve as pharmaceutically-acceptable carriers or components thereof are sugars, such as lactose, glucose and sucrose; starches, such as cornstarch and potato starch; cellulose and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose, cellulose acetate; powdered tragacanth; malt; gelatin; talc; solid lubricants, such as stearic acid, magnesium stearate; calcium sulfate; vegetable oils, such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil and oil of theobroma; polyols such as propylene glycol, glycerin, sorbitol, mannitol, and polyethylene glycol; alginic acid; emulsifiers, such as the Tweens®; wetting agents such as sodium lauryl sulfate; coloring agents; flavoring agents; excipients; tableting agents; stabilizers; antioxidants; preservatives; pyrogen-free water; isotonic saline; and phosphate buffer solutions.

The choice of a pharmaceutically-acceptable carrier to be used in conjunction with a compound is basically determined by the way the compound is to be administered. The compounds of the present invention may be administered systemically. Routes of administration include transdermal; oral; parenterally, including subcutaneous or intravenous injection; topical; and/or intranasal.

The appropriate amount of the compound to be used may be determined by routine experimentation with animal models. Such models include, but are not limited to the intact and ovariectomized rat models, the ferret, canine, and non human primate models as well as disuse models.

Preferred unit dosage forms for injection include sterile solutions of water, physiological saline, or mixtures thereof. The pH of said solutions should be adjusted to about 7.4. Suitable carriers for injection or surgical implants include hydrogels, controlled- or sustained release devices, polylactic acid, and collagen matrices.

Suitable pharmaceutically-acceptable carriers for topical application include those suited for use in lotions, creams, gels and the like. If the compound is to be administered perorally, the preferred unit dosage form is tablets, capsules and the like. The pharmaceutically-acceptable carriers suitable for the preparation of unit dosage forms for oral administration are well-known in the art. Their selection will depend on secondary considerations like taste, cost, and shelf stability, which are not critical for the purposes of the subject invention, and can be made without difficulty by those skilled in the art.

#### **Methods of Use**

The compounds of the present invention are useful in treating many medical disorders, including for example, ocular disorders, hypertension, fertility control, nasal congestion, neurogenic bladder disorder, gastrointestinal disorders, dermatological disorders, and osteoporosis.

The compounds of the present invention are useful in increasing bone volume and trabecular number through formation of new trabeculae, increasing bone mass while maintaining a normalized bone turnover rate, and formation of bone at the endosteal surface without removing bone from the existing cortex. Thus, these compounds are useful in the treatment and prevention of bone disorders.

The preferred routes of administration for treating bone disorders are transdermal and intranasal. Other preferred routes of administration include rectal, sublingual, and oral.

The dosage range of the compound for systemic administration is from about 0.01 to about 1000  $\mu\text{g/kg}$  body weight, preferably from about 0.1 to about 100  $\mu\text{g/kg}$  per body weight, most preferably from about 1 to about 50  $\mu\text{g/kg}$  body weight per day. The transdermal dosages will be designed to attain similar serum or plasma levels, based upon techniques known to those skilled in the art of pharmacokinetics and transdermal formulations. Plasma levels for systemic administration are expected to be in the range

of 0.01 to 100 nanograms/ml, more preferably from 0.05 to 50 ng/ml, and most preferably from 0.1 to 10 ng/ml. While these dosages are based upon a daily administration rate, weekly or monthly accumulated dosages may also be used to calculate the clinical requirements.

Dosages may be varied based on the patient being treated, the condition being treated, the severity of the condition being treated, the route of administration, etc. to achieve the desired effect.

The compounds of the present invention are also useful in decreasing intraocular pressure. Thus, these compounds are useful in the treatment of glaucoma. The preferred route of administration for treating glaucoma is topically.

### **Composition and Method Examples**

The following non-limiting examples illustrate the subject invention. The following composition and method examples do not limit the invention, but provide guidance to the skilled artisan to prepare and use the compounds, compositions and methods of the invention. In each case other compounds within the invention may be substituted for the example compound shown below with similar results. The skilled practitioner will appreciate that the examples provide guidance and may be varied based on the condition being treated and the patient.

#### **Example A**

Pharmaceutical compositions in the form of tablets are prepared by conventional methods, such as mixing and direct compaction, formulated as follows:

<u>Ingredient</u>	<u>Quantity (mg per tablet)</u>
Compound of Example 1	5
Microcrystalline Cellulose	100
Sodium Starch Glycollate	30
Magnesium Stearate	3

When administered orally once daily, the above composition substantially increases bone volume in a patient suffering from osteoporosis.



**Example B**

Pharmaceutical compositions in liquid form are prepared by conventional methods, formulated as follows:

<u>Ingredient</u>	<u>Quantity</u>
Compound of Example 1	5 mg
Phosphate buffered physiological saline	10 ml
Methyl Paraben	0.05ml

When 1.0 ml of the above composition is administered subcutaneously once daily, the above composition substantially increases bone volume in a patient suffering from osteoporosis.

**Example C**

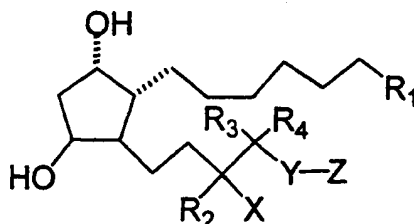
Topical pharmaceutical compositions for lowering intraocular pressure are prepared by conventional methods and formulated as follows:

<u>Ingredient</u>	<u>Amount (wt %)</u>
Compound of Example 38	0.004
Dextran 70	0.1
Hydroxypropyl methylcellulose	0.3
Sodium Chloride	0.77
Potassium chloride	0.12
Disodium EDTA (Edetate disodium)	0.05
Benzalkonium chloride	0.01
HCL and/or NaOH	pH 7.2-7.5
Purified water	q.s. to 100%

While particular embodiments of the subject invention have been described, it would be obvious to those skilled in the art that various changes and modifications to the compositions disclosed herein can be made without departing from the spirit and scope of the invention. It is intended to cover, in the appended claims, all such modifications that are within the scope of this invention.

What is claimed is:

1. A compound having the structure:



characterized in that

- (a)  $R_1$  is  $\text{CO}_2\text{H}$ ,  $\text{C}(\text{O})\text{NHOH}$ ,  $\text{CO}_2\text{R}_5$ ,  $\text{CH}_2\text{OH}$ ,  $\text{S}(\text{O})_2\text{R}_5$ ,  $\text{C}(\text{O})\text{NHR}_5$ ,  $\text{C}(\text{O})\text{NHS}(\text{O})_2\text{R}_5$ , or tetrazole; characterized in that  $\text{R}_5$  is alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring;
- (b)  $\text{R}_2$  is H or lower alkyl;
- (c) X is  $\text{NR}_6\text{R}_7$ ,  $\text{OR}_8$ ,  $\text{SR}_9$ ,  $\text{S}(\text{O})\text{R}_9$ ,  $\text{S}(\text{O})_2\text{R}_9$ , or F; characterized in that  $\text{R}_6$ ,  $\text{R}_7$ , and  $\text{R}_8$  are independently selected from the group consisting of H, acyl, alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, and heteroaromatic ring; and characterized in that  $\text{R}_9$  is alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring;
- (d)  $\text{R}_3$  and  $\text{R}_4$  are independently H,  $\text{CH}_3$ ,  $\text{C}_2\text{H}_5$ ,  $\text{OR}_{10}$ ,  $\text{SR}_{10}$ , or OH, except that both  $\text{R}_3$  and  $\text{R}_4$  are not OH; characterized in that  $\text{R}_{10}$  is alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring,  $\text{R}_{10}$  having from 1 to about 8 member atoms;
- (e) Y is  $(\text{CH}_2)_n$ ; n being an integer from 0 to about 3;

- (f) Z is carbocyclic aliphatic ring, heterocyclic aliphatic ring, monocyclic heteroaromatic ring, or substituted phenyl when n is 0, 2, or 3; and Z is carbocyclic aliphatic ring, heterocyclic aliphatic ring, or substituted phenyl when n is 1; and

any optical isomer, diastereomer, enantiomer of the above structure, or a pharmaceutically-acceptable salt, or biohydrolyzable amide, ester, or imide thereof.

2. The compound according to Claim 1 characterized in that  $R_1$  is selected from the group consisting of  $\text{CO}_2\text{H}$ ,  $\text{C}(\text{O})\text{NHOH}$ ,  $\text{CO}_2\text{CH}_3$ , and  $\text{CO}_2\text{C}_3\text{H}_5$ .
3. The compound according to Claim 2 characterized in that  $R_2$  is H or  $\text{CH}_3$ .
4. The compound according to Claim 3 characterized in that X is OH.
5. The compound according to Claim 1, 2, 3, or 4 characterized in that n is 0, 2, or 3 and Z is substituted phenyl or heteroaromatic ring.
6. The compound according to Claim 5 characterized in that Z is substituted phenyl or substituted or unsubstituted thienyl.
7. The compound according to Claim 6 characterized in that n is 2.
8. The compound according to Claim 1, 2, 3, or 4 characterized in that n is 1 and Z is substituted phenyl, said substituents being selected independently from the group consisting of halo, alkyl, haloalkyl, cyano, nitro, alkoxy, phenyl, and phenoxy.
9. The use of a compound according to any of the preceding claims in the manufacture of a medicament for treating a bone disorder in a human or other mammal.

10. The use of Claim 9 characterized in that said bone disorder is osteoporosis.

# INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 98/18340

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 6 C07C405/00 //A61K31/557

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 011 262 A (HESS HANS-JURGEN E ET AL) 8 March 1977 see column 34, line 45 - line 53 ---	1-8
X	G.L. BUNDY ET AL.: "Synthesis of 17-phenyl-18,19,20-trinorprostaglandins I. The PG1 series." PROSTAGLANDINS, vol. 9, no. 1, January 1975, pages 1-4, XP002084674 STONEHAM, MA US cited in the application see page 3 ---	1-8
X	DE 24 09 460 A (ONO PHARMACEUTICAL CO) 29 August 1974 see claims --- -/--	1-8

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

17 November 1998

Date of mailing of the international search report

08/12/1998

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Berte, M

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 98/18340

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DE 27 37 808 A (PFIZER) 16 March 1978 see claims ---	
X	DE 23 65 101 A (SCHERING AG) 10 July 1975 see claims ---	1-8
X	DE 23 55 731 A (PFIZER) 22 May 1974 see claims ---	1-8 1-9
P,X	US 5 703 108 A (ROSATI ROBERT L ET AL) 30 December 1997 see claims ---	1,9
X	US 4 621 100 A (LUND JOHN E ET AL) 4 November 1986 see claims ---	9 1-9
X	WO 95 18102 A (ALLERGAN INC) 6 July 1995 see claims ---	1-8
X	WO 97 23225 A (ALCON LAB INC) 3 July 1997 see page 16, line 6 - page 17, line 3 -----	1-9

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/18340

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4011262 A	08-03-1977	AR 209064 A	31-03-1977
		AR 214383 A	15-06-1979
		AT 367033 B	25-05-1982
		AT 620773 A	15-10-1981
		AT 366060 B	10-03-1982
		AT 987276 A	15-07-1981
		AT 352920 B	10-10-1979
		AT 987476 A	15-03-1979
		AT 359659 B	25-11-1980
		AU 5778473 A	09-01-1975
		BE 802231 A	14-01-1974
		CA 1041495 A	31-10-1978
		CH 593275 A	30-11-1977
		CH 593963 A	30-12-1977
		CH 593991 A	30-12-1977
		CH 593932 A	30-12-1977
		CH 593254 A	30-11-1977
		CS 201027 B	31-10-1980
		CS 201028 B	31-10-1980
		CS 201029 B	31-10-1980
		CS 201030 B	31-10-1980
		DD 109210 A	20-10-1974
		DD 116459 A	20-11-1975
		DE 2353159 A	13-03-1975
		DE 2365767 A	15-04-1976
		DE 2334945 A	07-03-1974
		DK 137179 A	03-04-1979
		DK 137479 A	03-04-1979
		FI 57583 B	30-05-1980
		FI 790070 A	10-01-1979
		FI 790071 A	10-01-1979
		FI 790072 A	10-01-1979
		FR 2192834 A	15-02-1974
		FR 2361381 A	10-03-1978
		FR 2361410 A	10-03-1978
		GB 1446342 A	18-08-1976
		GB 1446343 A	18-08-1976
		GB 1446344 A	18-08-1976
		GB 1446341 A	18-08-1976
		IE 37909 B	09-11-1977

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/18340

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4011262 A		IE 37910 B	09-11-1977
		IE 37911 B	09-11-1977
		IE 37912 B	09-11-1977
		IN 138789 A	03-04-1976
		JP 914649 C	21-07-1978
		JP 49092053 A	03-09-1974
		JP 52041257 B	17-10-1977
		JP 52097958 A	17-08-1977
		JP 52122349 A	14-10-1977
		JP 52093753 A	06-08-1977
DE 2409460 A	29-08-1974	JP 1134074 C	14-02-1983
		JP 49109353 A	17-10-1974
		JP 57020305 B	27-04-1982
		AU 6608974 A	28-08-1975
		BE 811665 A	17-06-1974
		FR 2218899 A	20-09-1974
		GB 1464916 A	16-02-1977
		NL 7402663 A	30-08-1974
		US 3966792 A	29-06-1976
		ZA 7401286 A	26-02-1975
DE 2737808 A	16-03-1978	BE 858147 A	27-02-1978
		DK 379477 A	28-02-1978
		FR 2362849 A	24-03-1978
		GB 1542569 A	21-03-1979
		IE 46257 B	20-04-1983
		JP 1059027 C	25-08-1981
		JP 53028159 A	16-03-1978
		JP 55039554 B	13-10-1980
		LU 78037 A	23-05-1979
		NL 7709444 A	01-03-1978
DE 2365101 A	10-07-1975	AU 7658674 A	24-06-1976
		BE 823692 A	20-06-1975
		DK 667774 A	25-08-1975
		FR 2255062 A	18-07-1975
		JP 50095269 A	29-07-1975
		NL 7416806 A	24-06-1975
		SE 7416037 A	23-06-1975



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

CT/US 98/18340

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 2365101 A		US 4004020 A	18-01-1977
DE 2355731 A	22-05-1974	AT 352754 B	10-10-1979
		AT 521876 A	15-03-1979
		AT 345999 B	10-10-1978
		AT 941073 A	15-02-1978
		AU 6230273 A	08-05-1975
		BE 807046 A	08-05-1974
		CA 1033727 A	27-06-1978
		CA 1052781 A	17-04-1979
		CA 1053669 A	01-05-1979
		CH 593933 A	30-12-1977
		CH 587283 A	29-04-1977
		CH 593930 A	30-12-1977
		DE 2365320 A	10-10-1974
		DK 90679 A	05-03-1979
		DK 90779 A	05-03-1979
		DK 143499 B	31-08-1981
		FI 58912 B	30-01-1981
		FR 2205338 A	31-05-1974
		FR 2286147 A	23-04-1976
		FR 2291200 A	11-06-1976
		GB 1456839 A	24-11-1976
		GB 1456840 A	24-11-1976
		GB 1456838 A	24-11-1976
		IE 40044 B	28-02-1979
		IE 40045 B	28-02-1979
		IE 40043 B	28-02-1979
		IN 143298 A	29-10-1977
		IN 142581 A	30-07-1977
		IN 139265 A	29-05-1976
		JP 1125139 C	30-11-1982
		JP 49133357 A	21-12-1974
		JP 57014347 B	24-03-1982
		NL 7315307 A	10-05-1974
		SE 412229 B	25-02-1980
		SE 7612261 A	03-11-1976
		SE 7612262 A	03-11-1976
		SE 417957 B	27-04-1981
		SE 7701523 A	10-02-1977

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/18340

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 2355731 A		SU 667131 A SU 704456 A US 4152527 A ZA 7308595 A	05-06-1979 15-12-1979 01-05-1979 25-09-1974
US 5703108 A	30-12-1997	NONE	
US 4621100 A	04-11-1986	JP 2016288 B JP 58029710 A	16-04-1990 22-02-1983
WO 9518102 A	06-07-1995	US 5545665 A AU 696645 B AU 1335995 A CA 2180008 A EP 0737184 A JP 9507228 T US 5587391 A US 5681848 A US 5798378 A	13-08-1996 17-09-1998 17-07-1995 06-07-1995 16-10-1996 22-07-1997 24-12-1996 28-10-1997 25-08-1998
WO 9723225 A	03-07-1997	AU 7680096 A	17-07-1997